REMARKS

FORMAL MATTERS:

Claims 2-5, 7-14, 18-24 and 26-31 are pending after entry of the amendments set forth herein.

Claims 1, 6, 15-17, and 25 have been are canceled without prejudice.

Claims 2-4, 8-14, and 19-20 are amended. Support for these amendments is found throughout the specification and particularly at, for example, page 8, lines 17-20; page 8, lines 23-27; page 10, lines 9-11; and page 15, lines 12-13.

No new matter has been added.

INTERVIEW SUMMARY

Applicants are grateful to Examiner Yaen for the telephonic interview conducted with the undersigned and with Michael Schiff, representative for the licensee, on December 21, 2005. The rejections of record were discussed, as were amendments presented here. The Examiner indicated that the proposed amendments accompanied by the arguments presented during the interview, which amendments and arguments are presented here, should obviate all rejections of record and place the application in form for allowance.

WITHDRAWAL OF REJECTIONS UNDER §112, ¶2

Applicants note with gratitude the withdrawal of the rejections of the claims under §112, ¶2.

REJECTIONS UNDER §102(B)

Claims 2-5, 8-10, 13, 19-20 and 24 were rejected as being anticipated by Kohler et al.[1] This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

Kohler et al. does not teach or suggest administering to a patient a composition comprising *alloactivated* lymphocytes from two or more *different human donors* who are each *unrelated* to the patient, as set out in independent claims 19 and 20.

During the interview, the Examiner pointed to Fig. 1 of Kohler et al. (at page 76) in support of the rejection. Applicants noted that the legend for Fig. 1 indicates that *alloactivated lymphocytes from*

[1] *Cancer Immunol. Immunother* (1988) 26:74-82.

only a single haploidentical related donor were used. In addition, the legend for Fig. 1 indicates these lymphocytes are alloactivated using a pool of *irradiated* unrelated lymphocytes in mixed lymphocyte culture (MLC).[2] As explained during the interview, irradiated lymphocytes are *inactivated* and *not capable of cell division.* Thus, the allogeneic lymphocytes present in the preparation are the *stimulator* cells only present to alloactivate the haploidentical cells. When administered to the patient, the haploidentical cells are the only non-irradiated cells in the preparation, which are designed to kill the tumor cells directly[3]. As indicated in the title, the object of the Kohler cells after administration is to kill the tumor directly by *adoptive immunotherapy.*

The premise behind the invention claimed in this patent application is fundamentally different. As explained throughout the specification, the therapeutic cells of this invention are not designed to be the direct effectors of the tumor rejection response. Without intending to be limited by theory, the therapeutic cells are alloactivated to a condition wherein they will secrete cytokines in an unrelated host, and thereby recruit participation of the host immune system, which in turn reacts against tumor antigen in a bystander response. The composition comprises a plurality of unrelated (HLA non-identical) cells which remain capable of proliferation in order to enhance the stimulation effect.

Thus, the invention claimed here is different from the system described by Kohler et al., in part because there are a plurality of unrelated responder cells that have not been inactivated. There is no motivation to adopt the Kohler system to arrive at the current invention, because of their stated purpose of adoptive immunotherapy. Kohler has a single effector cell population which is deliberately chosen to be haploidentical (i.e., related) to the treated subject to enhance direct killing. The unrelated donor cells in the preparation serve only the purpose of simulating the haploidentical cells, and are irradiated to prevent proliferation. Their purpose is finished before the composition is ever administered to the patient.

Withdrawal of this rejection is respectfully requested.

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[2] MLCs that use inactivated lymphocytes as stimulator cells are often referred to as a "one-way" MLC to signify that only one cell population -- the responder lymphocytes -- can become alloactivated.

[3] For further information on use of irradiated stimulator cells in a "one-way" MLC, see the specification as filed. See, e.g., specification page 12, lines 17-22 (discussing inactivated cells, including irradiated cells); page 18, lines 1-12 (discussing one-way MLC using inactivated stimulator cells).

REJECTIONS UNDER §103(A)

Claims 2-4, 7, 9, 10, 13, 17-24, 26 and 27-30 were rejected as being obvious over Kruse et al.[4] This rejection is respectfully traversed as applied and as it may be applied to the pending claims.

As discussed during the interview, Kruse et al. does not teach or suggest administering to a patient a composition comprising *alloactivated* lymphocytes from two or more *different human* donors who are each unrelated to the patient, as set out in independent claims 19 and 20. Instead, Kruse at best only describes a *single* allogeneic donor.

Independent claims 21 and 22 require administration of allogeneic lymphocytes *and* a tumor associated antigen. Kruse fails to teach or suggest administration of a composition containing *both* allogeneic lymphocytes *and* tumor associated antigen. As discussed during the interview, a detailed analysis of the experiment and results presented in Table 3 of Kruse et al. reveals that, in fact, at no time do the authors describe administration of allogeneic lymphocytes *and* tumor associated antigen. The table below provides an analysis of the experiment in Kruse:

[4] *Proc. Natl. Acad. Sci USA* (1990) 87:9577-9581.

Kruse et al., *Proc. Natl. Acad. Sci USA* (1990) **87**:9557-9581, page 9579

Host	Tumor	Treatment	Tumor antigen in therapeutic cell population	# of allogeneic donors in therapeutic cell population	Survival Time (days)
Fischer	9L (Fischer)	None (control)	none	0	20.2
Fischer	9L (Fischer)	IL-2	none	0	20.3
Fischer	9L (Fischer)	Fischer lymphocytes [5] + IL2	none	0	21.9
Fischer	9L (Fischer)	Fisher IL-2-activated lymphocytes [6] + IL-2	none	0	26.0
Fischer	9L (Fischer)	Fisher IL-2-activated lymphocytes [7] + IL-2	none	0	27.0
Fischer	9L (Fischer)	Fischer anti-9L tumor + IL-2	(uncertain) [8]	0	23.8
Fischer	9L (Fischer)	DA anti-Fischer alloactivated lymphocytes + IL-2	none	1	37.7

The *only* experiment in which an allogeneic lymphocytes were administered — the DA anti-Fischer lymphocytes in the last line of Table 3 (summarized in the last line of the table above) — did not involve use of tumor antigen *at all.* Instead, the DA lymphocytes *were activated against Fischer, not tumor.* There is simply no teaching or suggestion to administer a composition containing *both* an allogeneic lymphocyte *and* a tumor antigen.

Withdrawal of this rejection is respectfully requested.

[5] "Syngeneic lymphocytes" are genetically identical to the host, and thus are Fischer lymphocytes.

[6] Non-adherent LAK ("lymphokine activated killer") cells were syngeneic to the Fischer host. See Kruse et al. page 9579, col. 1, 2nd full paragraph, lines 9-12.

[7] Adherent LAK cells, like non-adherent LAK cells, were prepared from Fischer rats, and thus were syngeneic to the Fischer host. See, e.g., Kruse et al. page 9578, col. 1, last paragraph, lines 3-6.

[8] Tumor cells or tumor antigen is not used in the preparation of *any* of the cell populations, except for the cell population activated with the 9L tumor cell line. In this case, the tumor cells were used as stimulators in the activation process. Even assuming *arguendo* that some of the antigen survived the washing steps prior to administration, this population is different from the claimed invention because there are no allogeneic cells present — both the responder and the tumor cells are syngeneic to the treated animals.

OBVIOUSNESS-TYPE DOUBLE PATENTING

The rejections of certain claims under the judicially created doctrine of obviousness-type double patenting was maintained as set forth in the prior Office Action.

Specifically, as set out in the Office Action mailed October 20, 2004:

1) Claims 2-5, 7-14, 17-24 and 26 were rejected as being unpatentable over claims 1-18 of U.S. Pat. No. 6,203,787.

2) Claims 21, 22, 24 and 26 were rejected as being unpatentable over claims 1-34 of U.S. Pat. No. 6,207,147.

The Examiner indicated that claims 27-31 were similarly rejected on this ground.

Without acquiescing as to the grounds of the rejection, Applicants submit Terminal Disclaimers with this response to obviate this rejection. Applicants note that the filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection.[9]

Withdrawal of these rejections is respectfully requested.

[9] *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991) (stating that the "filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection.")

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number IRVN-005CIP.

Respectfully submitted,
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Date: Jan 12, 2006

By: _____
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Enclosure(s): Terminal Disclaimers

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